Remarks

I. The Claims

Upon entry of the foregoing amendment, claims 1, 3, 7, 9-15 and 17-20 are pending in the application, with claims 1 and 17 being the independent claims. Claims 1, 7, 14, 15, 17 and 19 are sought to be amended. Claim 16 is sought to be cancelled. Claim 20 is sought to be added. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Support for the amendment of claims 1 and 17 can be found, *inter alia*, throughout the specification, *e.g.*, page 8, lines 4-8 and 14-15; page 17, line 32 to page 18, line 12; page 31, line 13 to page 32, line 4; Figures 5-7; and original claim 16.

Support for new claim 20 can be found, *inter alia*, throughout the specification, *e.g.*, original claim 15.

II. Finality of Office Action Should Be Withdrawn

The Examiner states "Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL." (Office Action, page 24.) Applicants respectfully disagree.

The M.P.E.P states,

> [u]nder the principles of compact prosecution, each claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of the application, even if one or more claims are found to be deficient with respect to some statutory requirement. Thus, USPTO personnel should state all reasons and bases for rejecting claims in the first Office action.

(M.P.E.P § 2106(II).) Additionally, the M.P.E.P. states,

> [a] second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed.

(M.P.E.P § 706.07(a).)

In the previous Non-Final Office Action, dated January 11, 2005, claim 1 was rejected under 35 U.S.C. § 102(a) while claim 8 was not. In Reply, Applicants amended claim 1 to incorporate all of the elements of claim 8. In the subsequent Final Office Action, the Examiner rejected the amended claim 1 under 102(a). This clearly is a new rejection, since previous claim 8 was not rejected under 35 U.S.C. § 102(a) and the amended claim 1 had the same scope as previous claim 8. Therefore, the finality of the subsequent Office Action is improper.

Additionally, many of the documents cited by the Examiner to allegedly support a rejection under 35 U.S.C § 112, first paragraph, were not cited in preceding Office Actions, *e.g.*, Wang *et al.*, Kelland, Voskoglou-Nomikos *et al.*, Saijo *et al.*, Schuh, Bibby, and Peterson *et al.* (Office Action, page 12-15.) Therefore, Applicants find themselves having to respond after final and address references that were not applied by the Examiner in a previous Office Action. This is contrary to the Office's policy of compact prosecution.

Furthermore, the Examiner even lists the rejection of claims 1, 3, 7 and 9-19 under 35 U.S.C. § 112, first paragraph, under the heading of "*New Grounds of Rejection*". (Office Action, page 9.) However, there are no reasons given as to how "Applicants' amendment necessitated the new ground(s) of rejection". (Office Action, page 24.)

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the finality of the Office Action.

III. Filing dates of Applicants' Prior Amendment and Response

For clarity, Applicants note that the Examiner refers to Applicants' "amendment filed on 7-12-2005 and the responses filed on 7-12-2005 and 7-15-2005". However, Applicants' point out that they were filed on July 11, 2005 and July 14, 2005, respectively. Applicants' representative, Lewis J. Kreisler, signed Certificates of Mailing Under 37 CFR 1.8 certifying that the amendment and responses were being deposited with the United States Postal Service on July 11, 2005 and July 14, 2005, respectively.

IV. Double Patenting Rejection Should be Withdrawn

The Examiner states,

> [t]he provisional rejection of claims 1 and 4-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 6-9 of copending Application No. 10/717,101 is maintained for reasons of record.

(Office Action, page 3.)[1] Applicants note that Application No. 10/717,101 has issued as U.S. Patent No. 7,192,580. Additionally, Applicants note that as of December 6, 2006 (the date of the outstanding Office Action), the status of claims 2 and 6-9 of Application No, 10/717,101 was listed as canceled. Therefore, Applicants only address this rejection with regards to claim 1 of Applicants' present application and claim 1 of Application No. 10/717,101 as issued in U.S. Patent No. 7,192,580.

Applicants have herein amended claim 1 to incorporate some of the elements of previous dependent claim 16, which has not been rejected for double patenting. Claim 1 as amended herein relates to, *inter alia*, methods of reducing the viability of a tumor cell comprising administering to the tumor cell a vesicular stomatitis virus, wherein said tumor cell is a melanoma cell, wherein the virus is contained in a cell infected with the virus and wherein the administering comprises administering the virus-infected cell. In contrast, claim 1 of Application No. 10/717,101 (U.S. Patent No. 7,192,580) does not refer to or suggest administering a VSV-infected cell to a melanoma cell and therefore, does not render obvious claim 1 as presented herein.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the obviousness-type double patenting rejection.

V. Claim Rejections Under 35 U.S.C. § 102(a) Should be Withdrawn

The Examiner states, "claims 1, 14-15 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Roberts et al. (WO 99/18799)". (Office Action, page 5.)

---

[1] Applicants note that claims 4-6 were previously deleted in the Amendment filed July 11, 2005.

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice, or device. (See, *In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985).)

Claims 14 and 15 depend from claim 1. Applicants have herein amended claims 1 and 17 to recite "wherein the virus is contained in a cell infected with the virus and wherein the administering comprises administering the virus-infected cell." *Inter alia*, Roberts *et al.* does not disclose this element of the claim. Therefore, claims 1 and 17, and the claims that depend therefrom, are novel over Roberts *et al.*

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 14-15 and 17 under 35 U.S.C. § 102(a).

VI. Claim Rejections Under 35 U.S.C. § 103(a) Should be Withdrawn

The Examiner states,

> [t]he rejection of claim 16 rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (WO 99/18799 --IDS) in view of Molnar-Kimber et al. (W099/45783 --IDS) is maintained.

(Office Action, page 6.) Applicants respectfully disagree.[2]

Applicants have amended claims 1 and 17 to incorporate some of the elements of previous dependent claim 16. Claim 16 is cancelled herein. It is Applicants' position that Roberts *et al.* in view of Molnar-Kimber *et al.* does not render the presently claimed invention obvious. However, to the extent that the Examiner may attempt to apply this rejection to the claims herein, Applicants provide herewith a Declaration under 37 C.F.R. § 1.131.

Molnar-Kimber *et al.* published on September 16, 1999. The Declaration and accompanying Exhibit 1 show that the inventors conceived and reduced to practice the claimed

---

[2] Applicants' previous Remarks of July 11, 2005, when responding to the rejections under 35 U.S.C. §§ 102(a) and 103(a), stated that "[n]one of the cited references disclose or suggest an attenuated VSV." (page 23.) Applicants now hereby expressly retract this statement because it was incorrect. The incorrectness of this statement was unintentional. As the Examiner points out (Office Action, pages 5 & 6), Roberts *et al.* discloses attenuated VSV.

invention before September 16, 1999. As a result, Molnar-Kimber *et al.* is not prior art with regards to Applicant's invention as claimed herein.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103(a).

VII. Claim Rejections Under 35 U.S.C. § 112, first paragraph

A. Biological Deposit Is Not Required for Enablement

The Examiner has maintained the "rejection of claims 9-13 under 35 U.S.C. 112, first paragraph, for failing to meet the biological deposit requirements". (Office Action, page 8.) Applicants respectfully disagree. Applicants reiterate and incorporate by reference herein the remarks concerning this rejection that were made in Applicants' Amendment of July 11, 2005, pages 21-22 and the Supplemental Communication of July 14, 2005.

Even though the evidence presented previously and presented below conclusively support that the claimed invention meets the enablement requirements, Applicants remind the Examiner, with regards to an enablement rejection, "[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05 (eighth edition, September 2007); underlining in original.)

Applicants' presented evidence in their previous submissions that the viruses referred to in claims 9-13 are readily available to those in the art. In response, the Examiner states that "Applicant has failed to demonstrate that those viruses recited in the cited references constitute the same entities recited in the rejected claims." (Office Action, page 8.) Applicants respectfully disagree. As previously discussed (*e.g.*, see Applicants' Amendment of July 11, 2005, pages 21-22), Applicants' specification at page 10, lines 14-16, provides a key to the varying nomenclature in the art for these strains. Additionally, Example 27, Table 11, Figures 14-23 and the Sequence Listing of Applicants' specification provide both nucleic acid and amino acid information for viruses that are the subject matter of claims 9-13.

Therefore, Applicants have provided evidence that virus strains recited in claims 9-13 are readily available to those in the art. The Examiner has provided no evidence to the contrary, but

insists Applicants must demonstrate, at some higher level, that viruses in the scientific literature with the same nomenclature as in Applicants' specification are the same. This level of proof places an improper burden on Applicants. Applicants are unsure as to what other evidence the Examiner requires.

Applicants have presented *prima facie* evidence that the viruses recited in claims 9-13 are readily available in the art. Since the Examiner has provided no evidence to the contrary, the rejection is improper. In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 9-13 under 35 U.S.C. § 112, first paragraph.

B. The Claims Are Enabled

The Examiner states,

> [c]laims 1, 3, 7 and 9-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing attenuated VSV for reducing the viability of cell lines *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization [sic] attenuated VSV for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro*) or the utilization of said attenuated VSV to reduce the viability of a tumor cell in an immunocompetent animal.

(Office Action, pages 9-10.) Applicants respectfully disagree.

The purpose of the enablement requirement is to ensure that the specification describes the invention in such terms that one skilled in the art can make and use the invention commensurate with the scope of the claims. (*E.g.*, see MPEP § 2164.) The relevant inquiry for determining whether the scope of the claims is commensurate with the specification is "whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the claims." (*In re Moore*, 439 F.2d 1232, 1236 (CCPA 1971).)

The claims presented herein relate to, *inter alia*, methods of reducing the viability of a melanoma tumor cell. Even though the subject matter of the present claims encompasses wherein the claimed methods are "used to treat cancer" (Office Action, page 12.), there is no such limitation in any of the present claims. The Examiner's rejection improperly focuses on

enabling effective treatment of humans.[3] Whether or not a therapeutic reduction of tumor cell viability can be shown or predicted is not pertinent for meeting the enablement requirement with regards to the subject matter of the invention claimed herein, since these claims do not recite any limitations directly related to a therapeutic reduction of tumor cell viability.[3]

Additionally, Applicants refer the Examiner to *Ex parte* Saito and Zhao (Appeal No. 2005-1442 before the Board of Patent Appeals and Interferences (BPAI); Appendix 1) and *Ex parte* Boutin (Appeal No. 2006-1879 before the BPAI; Appendix 2), which both stand for the proposition that unless the claims explicitly refer to a therapeutic benefit, typically the Examiner should not determine if the claims are enabled for an unclaimed therapeutic benefit. In *Ex parte* Saito and Zhao the Board stated,

> the examiner may be correct that achieving clinically useful gene therapy using the claimed method would require undue experimentation, but the claims are not nonenabled merely for encompassing that difficult-to-achieve outcome.

(*Ex parte* Saito and Zhao, page 7.) In *Ex parte Boutin* the Board stated,

> [t]his appeal involves claims to a method of transferring nucleic acids into cells, which the examiner has rejected as nonenabled . . . . Because we conclude that enabling the claimed method does not require providing therapeutically effective gene therapy, we reverse.

(*Ex parte* Boutin, page 1.) The *Ex parte Boutin* decision also states,

> when the claims are not directed to a method that achieves a therapeutically useful result, achieving such a result is not required for the claims to be enabled . . . . Thus, while the claims read on gene therapy methods, they do not require producing a clinically effective therapeutic response.

(*Ex parte* Boutin, page 6.)

The claims presented herein refer to, *inter alia*, methods of reducing the viability of a melanoma tumor cell comprising administering to the tumor cell a vesicular stomatitis virus, wherein the virus is contained in a cell infected with the virus and wherein the administering comprises administering the virus-infected cell. At the time of filing, one skilled in the art, relying on the knowledge in the art and the teachings of Applicants' specification, would have been able to practice the presently claimed invention without undue experimentation, *e.g.*, *in*

---

[3] For clarity, Applicants believe that, if presented, similar claims to treating cancer would be enabled by the present application.

vitro, *ex vivo* and *in vivo*, even in a human. For example, one skilled in the art, upon review of the specification, would have been able to utilize numerous *in vitro* and *in vivo* methods for administering substances, including cells infected with a virus, to a melanoma tumor cell(s) without undue experimentation. The present specification clearly demonstrates that administering a VSV virus-infected cell to a melanoma tumor cell(s) would result in reducing the viability of the tumor cell(s). The Examiner has not presented any reasons or evidence to the contrary. The Examiner's rejection focuses on providing "support for the in vivo treatment of melanomas" (Office Action, page 16; underlining added), not on reducing the viability of a melanoma tumor cell(s) comprising administering a VSV virus-infected cell to the tumor cell(s).

Applicants believe that for the reasons above, the enablement rejection has been overcome. The Examiner has presented several articles that Applicants believe are presented with regards to the reliability of models in predicting clinical response, *e.g.*, Office Action, pages 12-15. However, as discussed above, clinical response is not pertinent for meeting the enablement requirement with regards to the subject matter of the invention claimed herein.[3]

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112, first paragraph.

Conclusion

It is not believed that extensions of time are required beyond those that may otherwise be provided for herein or in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, The United States Patent and Trademark Office is hereby authorized to charge any fee deficiency required to prevent abandonment of the current application or credit any overpayment to Deposit Account 50-1677.

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

/Douglas A. Golightly/
Douglas A. Golightly
Agent for Applicants
Registration No. 51,244
240-631-2500 ext. 3342

Date: January 7, 2008

Appendix 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte NORIMITSU SAITO and MING ZHAO

Appeal No. 2005-1442
Application No. 09/734,786

ON BRIEF

Before ELLIS, SCHEINER, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of introducing a nucleic acid into a subject by modifying and transplanting hair follicles. The examiner has rejected the claims as nonenabled. We have jurisdiction under 35 U.S.C. § 134. Because the examiner has not shown that undue experimentation would have been required to practice the claimed method, we reverse.

Background

The specification discloses that "histocultured tissues, including tissues containing hair follicles, can be successfully modified genetically ex vivo and then transplanted successfully into an intact mammalian subject. The success of the

modification is enhanced by treating the histocultured tissues with collagenase prior to genetic modification." Pages 2-3.

The specification states that

> [a]lthough it is advantageous to treat the cultured tissue with collagenase in order to enhance the ability of the tissue to accept heterologous nucleic acids, the treatment is not so severe as to destroy completely the integrity of the three-dimensional array.
>
> The three-dimensional histoculture can be assembled from any tissue, including skin, especially skin containing hair follicles, lymphoid tissue, or tumor tissue. The choice of tissue will depend on the nature of the treatment contemplated. . . .
>
> For example, hair follicles are useful recipients of genes intended to affect the growth or quality of hair, but also are able to produce immunogens and other products that may be useful to the organism taken as a whole.

Page 4.

The specification provides a working example in which DNA encoding green fluorescent protein (GFP) was introduced into hair follicles of histocultured mouse skin; the percentage of GFP-expressing hair follicles ranged from 22% to 67%. See pages 11-12. In a second working example, hair follicles in skin samples were transfected with GFP-encoding DNA and grafted onto recipient mice. The results showed that "the percentage of hair follicles with GFP fluorescence in collagenase-treated skin was 5.7 times greater than in hair follicles of untreated skin." Pages 14-15. Fluorescence was detected for at least 10 days after grafting. Figure 3B.

Discussion

1. Claim construction

Claims 1 and 11 are representative of the claims on appeal and read as follows:

1. A method to introduce a nucleic acid molecule into a mammalian subject which method comprises

transplanting into the dermis of said subject at least one hair follicle that has been modified ex vivo to contain said nucleic acid molecule.

11. A method to introduce a nucleic acid molecule into a mammalian subject which method comprises transplanting into the corresponding tissue of said mammal a histocultured intact tissue that has been modified ex vivo to contain said nucleic acid molecule;

wherein said histoculture has been treated with collagenase prior to modifying said tissue with the nucleic acid.

Thus, claim 1 is directed to a method of introducing a nucleic acid into a mammal by modifying a hair follicle ex vivo to contain the nucleic acid and transplanting the hair follicle to the mammal. Claim 1 does not explicitly require that the nucleic acid be expressed or provide any particular benefit to the mammal.

Claim 11 is similar to claim 1 but encompasses treating tissues other than hair follicles; in addition, claim 11 requires that the tissue be treated with collagenase before being modified with the nucleic acid.

2. Enablement

The examiner rejected claims 1-8, 11, 13-15, 17, and 19, all of the claims remaining, under 35 U.S.C. § 112, first paragraph, on the basis that the specification does not enable those skilled in the art to practice the claimed method without undue experimentation. The examiner considered the factors set out in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and concluded that

> [d]ue to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids and the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells using ex vivo gene transfer into histocultured organs or tissues, it would require undue experimentation to practice the instant invention.

Examiner's Answer, page 10

Appellants argue that the claims are directed to a method of genetically modifying tissues ex vivo and transplanting the modified tissue into a subject, and therefore do not require achieving therapeutic levels of gene expression. Appeal Brief, page 5. Appellants point to the specification's discussion of prior art techniques and working examples as guidance to those skilled in the art. Appellants assert that "[t]he pending claims are fully supported by the ample amount of knowledge available in the relevant art when the present application was filed and the guidance provided in the specification." Id., page 7.

We agree with Appellants that the examiner has not adequately shown that undue experimentation would have been required to practice the claimed method. The examiner bears the initial burden of showing that a claimed invention is nonenabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.").

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993). "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

The enablement analysis must be focused on the product or method defined by the claims. "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003).

Here, the examiner has acknowledged that the claims are not limited to therapeutic methods, but argues that because therapeutic methods are encompassed by the claims, such methods must be enabled in order for the full scope of the claims to be enabled. See the Examiner's Answer, page 12.

The examiner's reasoning is logical but not entirely consistent with the case law: enabling the "full scope" of a claim does not necessarily require enabling every embodiment within the claim. See, e.g., Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984): "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. . . . Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." Atlas Powder concerned claims to a product, not a method as here, but the same principle applies – a claimed method does not lack enablement merely because it cannot be practiced under some circumstances or to achieve some particular result.

In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999), is instructive. In Cortright, the applicant claimed a method of "treating scalp baldness with an antimicrobial to restore hair growth." Id. at 1355, 49 USPQ2d at 1465. The Board reversed a rejection for lack of utility, but entered a new rejection for lack of enablement, on the basis that "restor[ing] hair growth" required returning the user's hair to its original state (a full head of hair). See id. "Because Cortright's written description discloses results of only 'three times as much hair growth as two months earlier,' 'filling-in some,' and 'fuzz,' the board reasoned, it does not support the breadth of the claims." Id. at 1358, 49 USPQ2d at 1467.

The court disagreed with the Board's claim interpretation, holding that "one of ordinary skill would construe this phrase [restoring hair growth] as meaning that the claimed method increases the amount of hair grown on the scalp but does not necessarily produce a full head of hair." Id. at 1359, 49 USPQ2d at 1468. The court concluded that the claims, so construed, were enabled. Id.

As with the present claims, the claims in Cortright encompassed a method of obtaining results that might be difficult to achieve: here, therapeutically effective gene therapy; in Cortright, complete restoration of hair growth. However, as in Cortright, the present claims do not require that particular result: the present claims require only introducing or delivering a nucleic acid; Cortright's claims required only some restoration of hair growth.

The court in Cortright did not dispute the Board's conclusion that completely restoring hair growth using Bag Balm® would require undue experimentation. See id. at 1357, 49 USPQ2d at 1467. The court nonetheless concluded that the claimed method

was not nonenabled merely because it encompassed one difficult-to-achieve outcome. The same reasoning applies here: the examiner may be correct that achieving clinically useful gene therapy using the claimed method would require undue experimentation, but the claims are not nonenabled merely for encompassing that difficult-to-achieve outcome.

The claims are directed to methods of introducing a nucleic acid into a mammalian subject or delivering a nucleic acid to a hair follicle or intact tissue. The examiner has not adequately explained why the specification does not enable those skilled in the art to introduce a nucleic acid into a mammalian subject, or deliver a nucleic acid to a hair follicle or intact tissue, without undue experimentation. We therefore reverse the rejection for nonenablement.

REVERSED

Joan Ellis Administrative Patent Judge	)
Toni R. Scheiner Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Eric Grimes Administrative Patent Judge	)

EG/dym

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, CA 92130-2332

Appendix 2

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RAYMOND H. BOUTIN

Appeal No. 2006-1879
Application No. 10/010,114

ON BRIEF

Before SCHEINER, GRIMES, and LEBOVITZ, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of transferring nucleic acids into cells, which the examiner has rejected as nonenabled. We have jurisdiction under 35 U.S.C. § 134. Because we conclude that enabling the claimed method does not require providing therapeutically effective gene therapy, we reverse.

Background

Methods for delivering nucleic acids to cells in vivo face several problems: "persistence in the biophase of the organism for a sufficient time to reach the target cell; recognition of the target cell and means for mediating transport of the genetic material through the cell membrane and into the cytoplasm of the cell; avoidance of degradation

within the cell by the reticuloendothelial system; and transport to and through the nuclear membrane into the nucleus of the cell where transcription of the genetic material can take place." Specification, page 2, lines 5-14. The specification discloses a "multifunctional molecular complex for the transfer of a nucleic acid composition to a target cell comprising . . . : 1) said nucleic acid composition; 2) one or more cationic polyamine components . . . ; [and] 3) one or more endosome membrane disruption promoting components." Page 12, lines 2-9.

"The core, or backbone[,] of the transfer moiety is the cationic polyamine, containing between 3 and 12 amines." Page 23, lines 17-18. The function of the cationic polyamine is "to overcome the incompatibility arising from the hydrophilic nature of the nucleic acid molecule and the lipophilic nature of the cell membrane." Id., lines 20-23.

"The next component of the transfer moiety is the endosome membrane disruption promoting component. . . . This can either comprise one or more lipophilic long chain alkyl groups attached through one or more of the nitrogen atoms of said polyamine, or can comprise a bridging group . . . through which there is attached a fusogenic peptide, or cholic acid or cholesteryl or derivative compound." Page 25, lines 28-37. This component "prevent[s] degradation of the nucleic acid molecule in a lysosome," page 16, lines 27-28, by "permit[ting] the complex to escape from the endosome, whereupon it can migrate into the nucleus of the target cell, and release the nucleic acid composition, whose genetic information can then be transcribed within said nucleus." Page 34, lines 2-6.

Discussion

1. Claims

Claims 1, 2, 5-9, and 17-52 are on appeal. Claims 3 and 4 are also pending; claim 4 has been objected to but not rejected, and claim 3 has been withdrawn from consideration by the examiner.

Claim 1 is representative and reads as follows:

> 1. A method for the transfer of a nucleic acid composition to cells, comprising the step of introducing a multifunctional molecular complex into cells,
>
> wherein said multifunctional molecular complex comprises:
>
> A) a nucleic acid composition; and
> B) a transfer moiety comprising
>
> (i) one or more cationic polyamine components, wherein each cationic polyamine is non-covalently bound to said nucleic acid composition and comprises from three to twelve nitrogen atoms; and
>
> (ii) one or more endosome membrane disruption promoting components independently selected from (a) at least one lipophilic long chain alkyl group or (b) a fusogenic peptide, cholic acid or cholesterol group or a derivative thereof;
>
> wherein said multifunctional molecular complex transfers said nucleic acid composition to said cells.

Thus, claim 1 is directed to a "method for the transfer of a nucleic acid composition to cells." The claim is not limited to cells in culture or in a subject, so the claim encompasses both in vitro and in vivo methods. The claim comprises "introducing . . . into cells" a multifunctional complex comprising a nucleic acid composition; a cationic polyamine comprising three to twelve nitrogen atoms, noncovalently bound to the nucleic acid composition; and an endosome disrupting agent (which can be a

lipophilic long chain alkyl group, a fusogenic peptide, cholic acid, a cholesteryl group, or a derivative) attached to a nitrogen of the polyamine component via specified linkages.

2. Enablement

The examiner rejected claims 1, 2, 5-9, and 17-52 under 35 U.S.C. § 112, first paragraph, for nonenablement. The examiner focused on the aspect of the claimed method that involves transferring a nucleic acid encoding a therapeutic protein into cells.[1] The examiner concluded that the specification is enabling for a method of transferring a nucleic acid encoding a therapeutic protein into cells in vitro but is not enabling for the same method carried out in vivo. See the Examiner's Answer, page 3.

The examiner reasoned that "[t]he in vivo aspect of claims 1, 2, 5-9 and 17-52 is interpreted as gene therapy as the specification does not disclose a use for delivering a therapeutic protein other than for therapeutic purposes." Id. The examiner noted that the instant application has an effective filing date of September 28, 1994,[2] and cited several references as evidence that undue experimentation would have been required to successfully carry out gene therapy as of that date. Id., pages 4-6.

The examiner noted that the specification does not "disclose any particular DNA sequences that can be administered by applicant's claimed methods" to treat any specific disease. Id., page 6. The examiner summarized the most relevant working examples:

---

[1] The examiner restricted the claims based on the type of protein encoded by the transferred nucleic acid. See the restriction requirement mailed August 13, 2003. Appellant elected the claims directed to a method of transferring a nucleic acid encoding a therapeutic agent. See the paper filed September 11, 2003. The examiner has stated that "[b]ased on this election . . . claims 1, 2[,] 4-9, [and] 17-52, are interpreted as methods of delivering a therapeutic agent using applicant's novel multifunctional molecular complex." Examiner's Answer, pages 7-8.

[2] The instant application claims benefit under 35 U.S.C. § 120 of the filing date of application serial number 08/314,060, filed September 28, 1994.

> Example 11 teaches the expression of lacZ when a plasmid comprising a β-galactosidase gene complexed to a transfer moiety of the invention is injected into mouse thigh muscle. . . . Example 12 teaches the finding of hepatitis B [virus] surface antigen in the blood [of] mice injected i.v. with a multifunctional molecular complex comprising a plasmid containing a hepatitis B virus surface antigen gene complexed to a transfer moiety of the invention.

Id., pages 6-7. The examiner found that these examples did not provide sufficient guidance, however, because "in neither case does the expression of the delivered gene result in an alleviation of a symptom of any disease." Id., page 7.

Appellant argues that "[s]ince the claims do not require a therapeutic effect, Applicant need not demonstrate such an effect in order to enable the claimed subject matter." Appeal Brief, page 4. Appellant argues that he "need[ ] only establish that the application enable[s] one of ordinary skill in the art to make and use a method for transfer[ring] nucleic acid compositions to cells . . . without undue experimentation." Id. Appellant argues that the references cited by the examiner are not applicable because they describe different methods of delivering nucleic acids to cells. Id., page 5. Finally, Appellant relies on a declaration submitted under 37 CFR § 1.132, which is said to provide additional examples of in vivo transfer of nucleic acids using the claimed method. See id., pages 7-9

The examiner bears the initial burden of showing that a claimed method is not enabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.").

The invention that must be enabled to satisfy § 112 is the invention defined by the claims. See CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."). Thus, when the claims are not directed to a method that achieves a therapeutically useful result, achieving such a result is not required for the claims to be enabled.

Here, the claims, as restricted, are directed to a "method for the transfer of a nucleic acid composition [encoding a therapeutic agent] to cells." Thus, while the claims read on gene therapy methods, they do not require producing a clinically effective therapeutic response. Cf. In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999) (claims to a method of "treating scalp baldness" could be enabled even if the method did not produce a full head of hair).

The examiner argues, however, that the specification must teach those skilled in the art how to use the claimed method to produce a therapeutically useful result because

> the only use disclosed for in vivo delivery is [ ] for therapeutic purposes. . . . Thus, while the specification enables delivery and expression in cells in culture or cells in vitro, the method of delivering has no enabled use for delivery to cells in an animal, patient or subject[;] that is[,] in vivo. There is no evidence that the method results in sufficient delivery of a nucleic acid in vivo to offer a therapeutic effect. The specification offers no use for mere delivery of a therapeutic agent in vivo absent a therapeutic effect.

Examiner's Answer, page 8. As we understand it, the examiner does not dispute that the specification enables those skilled in the art to transfer nucleic acids into cells in

vivo, but she argues that transferring a nucleic acid encoding a therapeutic protein does not produce a useful result unless it confers a therapeutic benefit.

The examiner's reasoning highlights the incorporation into § 112 of the utility requirement of 35 U.S.C. § 101: to be enabled, a claimed method must be disclosed sufficiently to allow those skilled in the art to carry out the recited steps and, in addition, the result of the claimed method must have a specific and substantial utility. See In re Fisher, 421 F.3d 1365, 1378, 76 USPQ2d 1225, 1235 (Fed. Cir. 2005) ("It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101."); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) ("[S]urely Congress intended § 112 to pre-suppose full satisfaction of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention.").

The examiner's reasoning is logical but we do not agree that it applies to the instant claims. The specification describes experiments in which exogenous DNA was transferred, using the claimed method, to muscle cells and liver cells in vivo. See pages 77-78. The examiner has not disputed the accuracy of these working examples, but points out that the transferred DNAs did not encode therapeutic proteins and the specification does not describe therapeutically effective gene therapy.

The examiner has cited several references to show that clinical application of gene therapy faced many hurdles in 1994. The examiner has characterized the references as showing that delivering therapeutic genes to cells in vivo and ensuring

adequate expression of the gene products were major areas of unpredictability at the time of filing. See the Examiner's Answer, pages 4-6.

We can accept, for discussion purposes, (1) that the references show that using gene therapy to produce a therapeutically effective result would have required undue experimentation in 1994, and (2) that gene therapy is the only in vivo use disclosed in the specification for the claimed method. Even given those two premises, however, we do not agree that the evidence shows that the claimed method was not enabled as of its effective filing date.

As discussed above, the claims are not directed to a method of carrying out gene therapy, but to a method of transferring nucleic acids into cells. That is, the claimed method is directed to one step in, for example, a gene therapy method. The claimed method is disclosed to overcome some of the problems discussed in the references cited by the examiner. See the specification, pages 2 and 16:

> The problems faced by [nonviral vectors or carriers] include . . . means for mediating transport of the genetic material through the cell membrane and into the cytoplasm of the cell; avoidance of degradation within the cell by the reticuloendothelial system; and transport to and through the nuclear membrane into the nucleus of the cell where transcription of the genetic material can take place.
>
> . . .
>
> This multifunctional molecular complex comprises essentially the combination of two key elements, (I) the nucleic acid composition which it is desired to transfer to the target cell, and (II) the transfer moiety, which . . . comprises several components whose function is . . . ii) to overcome the incompatibility arising from the hydrophilic nature of the nucleic acid molecule and the lipophilic nature of the cell membrane so that the former can pass through the latter; and iii) to prevent degradation of the nucleic acid molecule in a lysosome of said target cell, by disrupting the pre-lysosome, endosome formation stage.

The examiner has stated that the in vitro embodiments encompassed by the claims are enabled, and has not disputed the accuracy of the specification's in vivo working examples. There seems to be no dispute, therefore, that the claimed method results in the transfer and expression of nucleic acids in targeted cells. We cannot agree that such a result must provide a therapeutic effect in order to be useful.

A method that overcomes some of the problems plaguing the field of gene therapy would seem to be a useful advance, even if the advance is incremental and does not resolve all of the problems facing the field. Such a method is useful to those skilled in the art even if it is not sufficient, by itself, to allow immediate practice of gene therapy. A method that enhances the efficiency of transfer of nucleic acids to cells in vivo, as the present method is said to do, provides a valid research tool that those skilled in the art could use in carrying out experiments involving transferring nucleic acids to cells in vivo.

The present claims are different from, for example, the invention at issue in In re Fisher, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The applicant in that case claimed expressed sequence tags (ESTs) from genes of unknown function. See id. at 1370, 76 USPQ2d 1231. The court concluded that "the claimed ESTs act as no more than research intermediates that may help scientists to isolate the particular underlying protein-encoding genes and conduct further experimentation on those genes. . . . Accordingly, the claimed ESTs are . . . mere 'object[s] of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." Id. at 1373, 76 USPQ2d 1231.

The Fisher court considered the applicant's argument that an EST is a research tool, like a microscope, but found the analogy inapt: "[A] microscope has the specific benefit of optically magnifying an object to immediately reveal its structure. One of the claimed ESTs, by contrast, can only be used to detect the presence of genetic material having the same structure as the EST itself. It is unable to provide any information about the overall structure let alone the function of the underlying gene." Id. at 1373, 76 USPQ2d 1231. The court concluded that "Fisher's asserted uses are insufficient to meet the standard for a 'substantial' utility under § 101." Id. at 1373, 76 USPQ2d 1231.

The ESTs at issue in Fisher lacked substantial utility because they were useful only for conducting experiments on the genes of which the ESTs were part; they were not useful for conducting research generally but only for conducting research to learn more about the ESTs themselves and the genes from which they were derived. Here, by contrast, the claimed method is broadly useful for transferring nucleic acids into cells. The instant claims are directed to a completed invention, not a "research intermediate" as in Fisher, that can be used to carry out research using a variety of nucleic acids, cells, and subjects. Thus, the instantly claimed method is a valid research tool that can be used to carry out research in general rather than research limited to discovering information about the claimed invention itself.

Summary

We do not agree with the examiner that enabling the instant claims requires enabling therapeutically effective gene therapy. The specification provides adequate guidance to enable those skilled in the art to use the claimed method to transfer nucleic

acids to cells, and that is all that the claims require. The rejection for lack of enablement is reversed.

REVERSED

Toni R. Scheiner Administrative Patent Judge	)
	) BOARD OF PATENT
Eric Grimes Administrative Patent Judge	) APPEALS AND
	) INTERFERENCES
Richard M. Lebovitz Administrative Patent Judge	)

EG/jlb

Howson and Howson
Cathy A. Kodroff
Suite 210
501 Office Center Drive
Ft Washington, PA 19034